REMARKS

Claims 1-26, 33-40 and 61-73 are pending in the application. Claims 27-32 and 41-60 have been canceled without prejudice. Claims 1-26, 33-36, 38-40, 61-69, and 72-73 are withdrawn from consideration. Claim 37 is currently amended to better clarify what applicants believe to be the invention. Support for the amendment can be found throughout the specification, and in particular on page 18, lines 9-10; in Figures 1-4, and in the corresponding description on pages 14-15; and on page 7, lines 21-34 continuing on to page 8, lines 1-2. New claim 74 has been added for consideration. Support for new claim 74 can be found in original claims 37 and 70. No issue of new matter is believed to be introduced by this amendment. Reconsideration of this application is respectfully requested.

Notice to Comply with Requirements for Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures

The Examiner alleges that the Sequence Listing fails to meet the requirements of 37 CFR 1.821 through 1.825. In particular, the application contains sequence disclosures in lines 24-25 on page 16, for which sequence identifiers are not provided. Applicants assert that the two sequences in lines 24-25 on page 16 correspond to SEQ ID NOS: 1 and 2, respectively, in the Sequence Listing submitted on September 23, 2002. Accordingly, Applicants assert that the submission of a Substitute Sequence Listing is not necessary. However, the paragraph on page 16, lines 18-33 has been amended to reflect the missing sequence identifiers as noted herewith. Applicants respectfully request withdrawal of this objection.

Specification

The Examiner objects to the Brief Description of the Drawings for Figure 3 on page 15 of the specification. In particular, the Examiner alleges that while the actual drawings identify the Figure as Figures 3a to 3j, the Brief Description on page 15 of the specification refers to the figure as Figures 3a-3d. The Examiner suggests that an amendment to the specification is necessary to correct this. Furthermore, references to the figure throughout the specification should be amended accordingly.

Applicants have amended the paragraph on page 15, lines 8-25 to correct the figure numbering in order to match the actual drawings submitted. Withdrawal of the objection is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph

Claims 37 and 70 are rejected under 35 U.S.C. 112, first paragraph. The Examiner alleges that the specification, while being enabling for a method of screening for HIV-1 macrophage tropic (HIV M-tropic) fusion inhibitors with cells expressing both CD4 and CCR5 in the presence of M-tropic HIV-1 infection or a virus pseudotyped with a full-length HIV M-tropic envelope protein, wherein the inhibitor can be used for treating a patient infected with a M-tropic HIV virus sensitive to the said inhibitor, does not reasonably provide enablement for a method of screening any or all HIV fusion inhibitors with a cell that only expresses CCR5 in the presence of any or all kinds of HIV isolates or any or all kinds of viruses pseudotyped with any or all kind of M-tropic envelope, wherein an inhibitor identified by the method can be used for prevention of AIDS. The Examiner alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner further alleges that the test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the application coupled with information known in the art without undue experimentation. The Examiner further alleges that it is well known in the art that the family of HIV-1 has tropisms. For example, the T-cell tropic HIV-1 virus only infects T-cells that express HIV-1 receptor CD4 and its fusion co-factor α-chemokine (or CXC chemokine) receptor, CXCR4. The M-tropic HIV-1 only infects macrophage or monocyte that expresses HIV-1 receptor CD4 and its fusion co-factor of β-chemokine (or CC-chemokine), CCR5 (Broder, *et al.* Pathology 1996, Vol. 64, No. 4, pp.171-179, see entire document). The Dual tropic primary HIV-1 isolate infects its target cell by using either the β-chemokine receptor CCR5 (synonym as CKR-5), CCR3 (synonym as CKR-5) or CCR2b (synonym as CKR-2b) (Doranz, *et al.* (Cell 1996, Vol. 85, pp. 1149-1158). Hence, the Examiner further alleges that different HIV-1 viruses use different chemokine receptors as their

fusion co-factor in conjunction with an HIV-1 binding receptor CD4 to fuse and infect the host cells. More particularly, the Examiner alleges that it is unpredictable for testing a CCR5 HIV-1 fusion inhibitor with a cell that only expresses CCR5 without CD4.

The Examiner alleges that this unpredictability is also demonstrated by applicants' own work published in Nature (Deng, *et al.* Nature 1996, Vol. 381, pp. 661-666, Fig. 2c on page 663) and the disclosure in the specification (See line 27 on page 1, and lines 15-18 on page 51 and lines 25-29 on page 48, lines 15-17 on page 51, Fig. 2C, Fig. 3A, Fig. 3I). The Examiner alleges that both Deng's publication and the specification teach that chemokine receptor CCR5 and receptor CD4 cooperatively mediated entry of M-tropic HIV (See examples 1-4). The Examiner further alleges that applicants do not teach that a cell line with only CCR5 (CC-CKR5) expression can be infected via T-tropic HIV-1 envelope mediated fusion. Applicants teach that the 3T3 cell with CD4 and CC-CKR5 expression cannot be infected with T-tropic HIV (HXB2 strain)(Fig. 3A).

Moreover, the Examiner alleges that the state of the art also teaches that the susceptibility of the monocytic THP-1 cell line to R5 (M-tropic, such as HIV-1 $_{Bal}$) or X4 (T-tropic, such as HIV-1 $_{IIIB}$) HIV-1 isolate infection depend on expression of CD4 rather than CCR5 or CXCR4 on the cell surface as evidenced by Konopka, et al. (AIDS RESEARCH AND HUMAN RETROVIRUSES 2002, Vol. 18, No. 2, pp. 123-131, see entire document, especially abstract, page 125, 3rd paragraph, Fig. 1 on page 127). Furthermore, the Examiner alleges that not all M-tropic envelope mediated fusion uses CCR5. Therefore, it is unpredictable for using a virus pseudotyped with any or all kinds of macrophage-tropic envelope protein to do the R5 mediated fusion inhibitor screening assay.

The Examiner alleges that the state of the art teaches that a fusion inhibitor such as T20 (enfuviritude, ENF) can be used for inhibiting HIV-1 envelope protein mediated fusion. However, HIV-1 viruses develop a resistance in response to a fusion inhibitor treatment. Therefore, it is unpredictable for using the inhibitor for preventing AIDS.

The Examiner alleges that the specification only teaches to use a cell line that expresses both CD4 and CCR5 infected with M-tropic HIV-1 virus or virus pseudotyped with the full-length M-tropic HIV-1 virus for doing the screening assay, and the inhibitor

identified by the method e.g. RANTES or MIP-1β will block the M-tropic HIV-1 envelope protein mediated fusion and inhibit the M-tropic HIV-1 infection. The Examiner alleges that the specification lacks teaching of any M-tropic HIV-1 fusion inhibitor that can be used for preventing AIDS.

The Examiner further alleges that the scope of the claims broadly read on the method for identifying an agent that can be used for treatment or prevention of AIDS comprising the use of all cells as long as they express CCR5 in any or all HIV infections or any virus pseudotyped with any or all M-tropic envelope proteins. The nature of the invention is an assay for screening for an agent that can be used for treating or preventing AIDS. Therefore, the Examiner alleges that the skill in the art to perform the full scope of the claims is quite high, especially in view of the unpredictability as described supra.

Applicants respectfully traverse the Examiner's rejection and have amended claim 37 whereby the method of identifying an agent to treat AIDS has been replaced with a method of identifying an agent that inhibits an HIV infection caused by a macrophage-tropic virus whose entry into cells is mediated by CCR5. Support for enablement of the claim as currently amended can be found throughout the specification, and particularly in the Example section on page 49, lines 14-17, and lines 19-23. Accordingly, in example 1 starting on page 46, Applicants created HIV virus stocks that were pseudotyped with various envelope proteins (HXB2 as a representative T-tropic Env and JRFL, ADA and BaL as macrophage-tropic Envs). These viral stocks were then used to infect cells which expressed various chemokine receptors. Viral entry into cells was monitored and it was determined that fusion and entry of viruses pseudotyped by macrophage tropic Env (JRFL, ADA and BaL) were inhibited by β chemokines, in particular, RANTES, MIP-1α and MIP-1β.

Accordingly, the preamble to claim 37 now reads:

"A method for selecting for an agent for possible use in the treatment and/or prevention of an HIV infection caused by a macrophage-tropic HIV virus, wherein entry of the macrophage-tropic virus into cells is mediated by CCR5, the method comprising the steps of:...."

Furthermore, claim 37 has also been amended to include CD4 (as well as CCR5) as a component of the cell used in the screening assay. The support for this amendment can be found on page 48, lines 10-29. Thus, step a) of claim 37 reads as follows:

"... (a) contacting an agent with a cell in the presence of a macrophage-tropic HIV virus or a virus pseudotyped with a macrophage-tropic envelope; wherein in the absence of the agent said cell undergoes fusion with and/or permits entry to the macrophage-tropic HIV virus or the virus pseudotyped with a macrophage-tropic envelope; wherein CCR5 and CD4 are components of the surface of said cell; and wherein said fusion or entry is mediated by CCR5..."

Thus, Applicants assert that claim 37, as currently amended, clearly points out that the screening method will identify agents that interfere with HIV entry into cells, in particular, a macrophage-tropic HIV, whereby fusion and entry of the virus into the cell is mediated by CCR5. Moreover, the claim further defines that the cell used in the screening method expresses both CCR5 and CD4.

Applicants further assert that the scope of the claim, as currently amended, is fully supported by the specification as filed. Based on the foregoing amendment to claim 37, withdrawal of the rejection is believed to be in order, and is respectfully requested.

The Examiner has rejected claim 6 because it is drafted as a reach-through claim and does not comply with the "how to make" prong of the enablement requirement for the reasons analyzed by weighting 7 factors outlined in Ex parte Forman.

Applicants respectfully traverse the Examiner's rejection and point out to the Examiner that claim 6 is not currently under examination and has been withdrawn from consideration. Thus, the rejection is improper and withdrawal is respectfully requested.

Non-Statutory Double Patenting

The Examiner has rejected claim 37 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-20 of U.S. patent number 6,258,527B1.

Applicants herewith file a Terminal Disclaimer, disclaiming the term of any patent granted on the instant application beyond that of the aforementioned patent. In light of the foregoing, withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §102 (a)

The Examiner has rejected claim 37 under 35 U.S.C. 102 (a) as being anticipated by Cocchi et al (Science 1995, Vol. 270, pp. 1811-1815) in light of Moriuchi et al. (J. Immunol. 1997, Vol. 159, pp. 5441-5449).

1. The Examiner's Position

The Examiner alleges that the claimed method for identifying an agent whether or not it can influence HIV-1, preferably M-tropic HIV-1 envelope fusion or entry into a target cell, said method comprising contacting an agent with a cell having a CCR5 expressed on the cell surface in the presence of an HIV virus or a virus pseudotyped with an HIV macrophage envelope and measuring whether the agent can significantly inhibit virus fusion with the target cell. If the inhibition is statistically greater, the agent is selected.

The Examiner alleges that Cocchi et al. teach a method for inhibiting HIV-1 infection comprising contacting the agent with recombinant human C-C chemokine selected from the group consisting of recombinant human RANTES (rhRANTES) or MIP-1α or MIP-1β or MCP-1 with a PM1 cell line in the presence of M-tropic HIV-1, or a T tropic HIV-1 virus. The Examiner alleges that the PM1 cell inherently expresses CCR in light of the disclosure of Moriuchi et al. and the M tropic HIV-1 inherently comprises the macrophage tropic envelope. The Examiner alleges that they demonstrate that the chemokines RANTES, MIP-1α , MIP-1β but not MCP-1 significantly inhibits the M-tropic HIV-1 infection. However, they do not inhibit the T tropic HIV-1 viral antigen expression. The Examiner further alleges that while the assay shown by Cocchi et al. is not a fusion assay, the results of the decreased M tropic virus infection inherently is the cause of the fusion inhibition by the chemokine RANTES or MIP-1α or MIP-1β. The Examiner alleges that the assay disclosed by Cocchi et al teach each of the limitations of claim 37 as originally drafted.

Furthermore, the Examiner alleges that while the mechanism of inhibition of HIV-1 M tropic virus infection by C-C chemokine, rhRANTES or MIP-1α or MIP-1β is certain because it is later recognized by the person skilled in the art that CCR5 is a fusion co-factor for M tropic HIV-1 envelope protein mediated fusion. The C-C chemokine RANTES or MIP-1α or MIP-1β is the CCR5 native ligand, which binds the CCR5 with much higher affinity. Therefore, the effect of using CCR5 ligand to inhibit the M tropic HIV-1 virus fusion and infection via blocking the fusion co-factor CCR5 will always happen and be accepted by a person skilled in the art post filing date of the current application. According to Feit et al, it is irrelevant whether the understanding was apparent at the time of filing the application in question.

2. Applicants' Response

Applicants respectfully traverse the rejection. The patent law is settled that a rejection under 35 U.S.C. §102 is proper only if a single reference discloses every single element of an invention as claimed. The patent law is also clear that in certain circumstances a reference need not expressly disclose every single element of an invention as claimed if the element is inherent in the disclosure of the prior art. However, the patent law is equally clear that certain conditions must be met before an element may be found to be inherent in the disclosure of a prior art reference. The Examiner correctly outlines these conditions as settled by the Federal Circuit citing the review article of Feit et al. (2003, J. Pat. Trade Off. Soc., Vol. 85, No. 1, pages 5-21). The three conditions are as follows:

1. Certainty. The prior art reference must ***necessarily*** and ***certainly*** result in the invention as claimed including the elements of the claimed invention that are not expressly disclosed by the reference.

2. Chronology. The prior art reference must ***always*** result in the invention as claimed including the elements of the claimed invention that are not expressly disclosed by the reference.

3. Recognition. One of ordinary skill must ***recognize*** that the elements of the claimed invention that are not expressly disclosed by the reference are present in the disclosure of the prior art reference.

Cocchi et al. do not meet a single of these three criteria as required by the law

Applicants respectfully point out to the Examiner that Cocchi et al. do not teach or suggest all of the limitations of claim 37 as currently pending, either expressly or inherently. The Examiner acknowledges that ***Cocchi et al. do not teach or suggest*** a method of selecting an agent for possible use in the treatment or prevention of an HIV infection caused by a macrophage-tropic HIV virus, ***wherein entry of the macrophage-tropic virus into cells is mediated by CCR5***, the method comprising contacting the agent with a cell in the presence of the macrophage tropic virus and monitoring whether the virus fuses with the cell in the absence of the agent but does not fuse with the cell in the presence of the agent. Therefore, not a single one of the foregoing requirements for a rejection based upon inherency are met regarding this element of the claimed invention. ***Cocchi et al. do not teach or suggest that chemokines such as RANTES, MIP-1 alpha or MIP-1 beta prevent the virus from fusing with the cell surface***, as recited in the currently amended claims. ***The role of CCR5 as a co-factor for viral fusion and entry into the cell was not known at the time the Cocchi et al. reference was published.*** Cocchi et al. clearly believed that the chemokines exerted their effect *subsequent* to viral entry. Moreover, Cocchi et al specifically state on page on page 1814 in the middle column, second paragraph:

> *"Chemokine-mediated control of HIV may occur either directly, through their inherent anti-lentiretroviral activity, or indirectly, through their ability to chemoattract T cells and monocytes in proximity of the infection loci."*

Therefore, not a single one of the foregoing three requirements for a rejection based upon inherency are met regarding this element of the claimed invention.

At the time the Cocchi et al. reference was published, ***the CCR5 receptor had not yet been identified, nor had its role as a co-factor with CD4 for viral entry into cells***

been elucidated. Therefore, given the lack of knowledge at the time of publication of the Cocchi et al. reference of the very existence of the CCR5 receptor, it certainly cannot be that one of skill in the art would recognize that this element of the invention as claimed was present in the teachings of Cocchi et al. Moreover, based upon the teachings of Cocchi et al. there would have been no motivation to screen for agents that block fusion of the HIV macrophage-tropic strains of virus to cells expressing both CD4 and CCR5.

3. The Examiner's non-specific rejection based upon a combination of reference

The Examiner also alleges that the claims of the present application are inherent based on the teachings of Cocchi et al. in view of Moriuchi et al. Applicants believe that the Examiner intends to reject the pending claims as unpatentable under 35 U.S.C. §103 though no such rejection is made. Applicants note that a rejection under 35 U.S.C. §103 may also rely upon inherent disclosure of elements of the invention as claimed that are not expressly taught by the prior art references. The law of inherency is the same as applied to a rejection under 35 U.S.C. §103 as it is when applied to a rejection under 35 U.S.C. §102.

4. Applicants' Response to the non-specific rejection based upon a combination of references

(a) The Examiner fails to set forth a proper prima facie case of obviousness

Applicants remind the Examiner that a rejection under 35 U.S.C. §103 is proper only when a prior art reference alone or in combination with a second prior art reference renders the invention obvious. Applicants further remind the Examiner that a rejection based upon a combination of references is not proper unless the following three criteria are met: 1) the references in combination teach every single element of the invention as claimed (the law of inherency may be applied for those elements not expressly disclosed by the references in combination); 2) there must be some suggestion or motivation in the prior art to combine the references to reach the invention as claimed; and 3) there must be a reasonable expectation of success in the making the combination to reach the invention as claimed.

Any alleged combination of references in the present situation fails the most basic test for the appropriateness of a rejection. The Examiner admits that Cocchi et al. do not teach or suggest the presence of a CCR5 receptor, and the Examiner admits that Moriuchi et al. is not prior art. The references simply cannot be combined.

(b) The Examiner confuses the relevant time of inquiry

The Examiner apparently offers Moriuchi et al. for the teaching of a CCR5 receptor. The Examiner is reminded that the patent law clearly states that

> A patent may not be obtained...if the difference between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious ***at the time the invention was made***... 35 U.S.C. §103.

Moriuchi et al published their findings after Applicants' earliest priority date. As such, Moriuchi et al. may not be used as a secondary reference for a rejection under 35 U.S.C. §103. Likewise, Moriuchi et al. may not be used as evidence of what was known in the art at the time Applicants' both made their invention and filed the instant patent application.

(c) The Examiner offers contradictory statements

The Examiner correctly summarizes the three criteria for inherency, the most important one being certainty, and certainty is established when the reference necessarily results in the claimed process as opposed to a possibility. Applicants respectfully point out to the Examiner that such certainty can be questioned if one takes into account the Examiner's own comments regarding unpredictability as well as the reference cited on page 6, paragraph 19 of the present Office Action (Igarashi et al. J. Virol. 2003, Vol. 13042-13052). In particular, as the Examiner notes:

> "...not all M-tropic envelope mediated fusion uses CCR5.....Therefore, it is unpredictable for using a virus pseudotyped with any or all kinds of macrophage-tropic envelope protein to do the R5 mediated fusion inhibitor screening assay."

Furthermore, with respect to the second criterion, that is, it will always happen, Applicants assert that once again, as the Examiner has pointed out, in some cases, it may not happen. That is, as the Examiner has noted on page 6, paragraph 19 in the present Office Action:

"...not all M-tropic envelope mediated fusion uses CCR5."

(d) The Examiner's colleagues have already settled the issues being discussed herein

Applicants respectfully direct the Examiner's attention to the file history for Applicants' previously issued patent, U.S. Patent 6,258,527, issued on July 10, 2001 from which the present application is a continuation application. Moreover, Applicants disclaim the patent term of the present application, which might extend beyond that of the subject patent U.S. 6,258,527 and enjoying a presumption of validity. The Examiner's colleague, Robert Budens from art unit 1648, expressly states in the file history in an Office Action dated August 31, 1999, on page 5 of Paper No. 14, that:

"The claimed invention appears free of the art. The art does not disclose or fairly suggest cell lines as set forth in claim 41 or methods of using such cell lines for identifying inhibitors of HIV infection."

Based on the foregoing, withdrawal of the rejection is respectfully requested.

Fees

A check in the amount of $65.00 is enclosed to cover the terminal disclaimer submitted herewith. No other additional fees are believed to be necessitated by the foregoing Response. However, should this be erroneous, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages.

Conclusions

Applicants believe that the foregoing arguments and amendments to the claims place the application in condition for allowance. Withdrawal of the rejections and objections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

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Attachments: One Interview Summary
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